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Birth weight, Early Life Course BMI, and Body Size Change: Chains of Risk to Adult Inflammation?

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Abstract

This paper examines how body size changes over the early life course predict high-sensitivity C-reactive protein in a U.S. based sample. Using three waves of the National Longitudinal Study of Adolescent Health (Add Health), we test the chronic disease epidemiological models of fetal origins, sensitive periods, and chains of risk from birth into adulthood. Few studies link birth weight and changes in obesity status over adolescence and early adulthood to adult obesity and inflammation. Consistent with fetal origins and sensitive periods hypotheses, body size and obesity status at each developmental period, along with increasing body size between periods, are highly correlated with adult CRP. However, the predictive power of earlier life course periods is mediated by body size and body size change at later periods in a pattern consistent with the chains of risk model. Adult increases in obesity had effect sizes of nearly .3sd, and effect sizes from overweight to the largest obesity categories were between .3–1sd. There was also evidence that risk can be offset by weight loss, which suggests that interventions can reduce inflammation and cardiovascular risk, that females are more sensitive to body size changes, and that body size trajectories over the early life course account for African American-and Hispanic-white disparities in adult inflammation.

Keywords

C-reactive protein; Inflammation; Birth Weight; Obesity; Fetal Origins; Chains of Risk; Sensitive Periods

Although a great deal of attention has been devoted to both the etiology and pathogenic consequences of obesity (Guh et al., 2009; Zeyda & Stulnig, 2009), understanding how patterns of body size stability and change over the early life course contribute to adult cardiovascular disease remains an important public health issue (Biro & Wien, 2010). Obesity is closely linked to comorbid conditions such as Type 2 diabetes, cardiovascular disease, and is a major contributor to lower U.S. life expectancy (Juonala et al., 2011; Kahn

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et al., 2006; Olshansky et al., 2005). Evidence suggests that chronic low-grade inflammation is a key pathway linking obesity to metabolic and CVD risk (de Heredia et al., 2012). Obesity-related inflammation increases pro-inflammatory cytokine production (i.e., IL-6 and TNFα) in adipose tissue, elevating acute phase inflammatory responses by way of C-reactive protein (CRP) produced in the liver (Tilg & Moschen, 2006). Moreover, chronically elevated CRP is associated with insulin resistance, Type 2 diabetes, and CVD (Van Gaal et al., 2006; Yudkin et al., 1999). Though links between harmful comorbid conditions and obesity are well documented (Guh et al., 2009), how body size across early life course periods predicts inflammatory markers linked to subsequent CVD outcomes remains largely unaddressed (though see Attard et al., 2013; Nazmi et al., 2009).

We assess four pathways by which body size over the early life course increases inflammation using the representative U.S.-based National Longitudinal Study of Adolescent Health (Add Health). The fetal origins hypothesis (or thrifty phenotype) proposes that insults during the biologically *sensitive period* in utero (e.g. growth restriction) alters offspring metabolic processes that shape long-term risk (Hales & Barker, 2001). Adolescence, a time of rapid physiological change via pubertal development intersecting with dramatic social change in the lives of youth (Crosnoe, 2011) creates an additional biologically sensitive period. In early adulthood, the acquisition of new social roles and environmental stressors can increase or solidify obesogenic health risk behaviors coupled with declines in overall self-rated health (Bauldry et al., 2012; Crosnoe & Elder, 2004) that marks an important *socially sensitive* period. These periods may also string together into "*chains of risk*" to shape current health as a consequence of correlated risks over time (Kuh et al., 2003; Lynch & Smith, 2004). We assess the contributions of these different pathways to adult inflammation among a cohort of youth first measured as adolescents in 1993–94 during a period of rising obesity and obesogenic morbidity (Lee, H. E., Lee, D., Guo, G., & Harris, K. M. 2011).

Literature Review

We examine the consequences of birth weight, obesity, and weight gain over the early life course for adult systemic inflammation as measured by high sensitivity CRP levels at ages 24 to 34. Obesity and adiposity are associated with elevated chronic inflammatory markers such as CRP (de Heredia et al., 2012) and may be tied to the accompanying risk of other obesity related conditions including metabolic dysregulation and cardiovascular disease (Hotamisligil, 2006; Zeyda & Stulnig, 2009). Given the dramatic weight gain trends in the U.S. at all age groups in recent years (Olshansky et al., 2005), and the generally poor birth weight profile of the U.S. relative to other developed nations, there are multiple hypothesized pathways for how body size is linked to health over the early life course. Figure 1 presents the pathways we assess. These pathways are denoted with *fetal origins* (birth) and adolescent *sensitive periods*, the socially disruptive transition to adulthood, and the *chains of risk* model capturing correlated risks over time.

Fetal Origins Hypothesis

Both low and high birth weight are markers of adverse fetal environments and birth weight has a U-shaped relationship to obesity, Type 2 diabetes, hypertension, and CVD (Fraser et

al., 2012; Seckl & Holmes, 2007). In the case of infant microsomia (<2500 g), poor nutrition and maternal stress levels restrict growth in-utero, altering glucose-insulin metabolic regulation while shaping subsequent growth patterns (Hales & Barker, 2001). Consequently, fetal growth restriction as measured by birth weight is associated with accelerated weight gain and increased intra-abdominal adiposity. Few studies measure the relationship between microsomia and adult inflammation, though lower birth weight may be associated with adult CRP (McDade et al., 2014; Nazmi et al., 2009; Tzoulaki et al., 2008). Although the links between macrosomia (>4000g), obesity, and Type 2 diabetes are beginning to receive attention, less is known about macrosomia and adult inflammation (Fraser et al., 2010). Infant macrosomia is linked to gestational diabetes, elevating the risk of adult obesity and Type-2 diabetes (Yessoufou & Moutairou, 2011). Moreover, macrosomic offspring have higher proinflammatory cytokine levels compared to normal birth weight offspring (Atègbo et al., 2006).

These pathways to CVD risk are shown in Figure 1. Assessing the degree to which microsomia/macrosomia are early life course sensitive periods that influence adult inflammation is the first goal of our analysis. Because birth weight differs by race/ethnic background in the U.S. (Martin et al., 2015), birth weight may be an important pathway by which social disadvantage shapes long-term health outcomes.

Adolescence to Adulthood: Biological and Socially Sensitive Periods

Later periods are also characterized by rapid physiological development and/or environmental change. As illustrated by Figure 1, adolescence is proposed as a high-risk period for obesogenic weight gain (Frederick et al., 2014). The confluence of developmental metabolic changes coupled with increased sedentary behavior and control over diet may combine to elevate adult metabolic and cardiovascular risk (Jasik & Lustig, 2008). Such change is particularly salient among females since abnormal weight gain in adolescence is associated with earlier onset of thelarche and menarche, two established correlates of adolescent obesity and adiposity (Wang et al., 2011). Adolescent boys' obesity is associated with later puberty onset (Solorzano & McCartney, 2010) and in both cases, adolescent obesity and adiposity predict adult obesity, Type 2 diabetes, hypertension, and CRP (Jasik & Lustig, 2008; May et al., 2012).

In addition to biologically sensitive periods, the transition to adulthood is a key period that may shape subsequent obesogenic risk for *social* reasons. This transition is a time of shifting demands when youth leave home, begin adopting adult roles, and acquire new stressors (Crosnoe & Elder, 2004). Consequently, there is considerable social change and physical activity further declines, fast-food intake increases, overall self-rated health declines (Bauldry et al., 2012; Jasik & Lustig, 2008; Larson et al., 2008), and BMI increases and becomes less likely to decrease (Gordon-Larsen et al., 2004a; Gordon-Larsen et al., 2004b). These trends of accumulated body size and recent weight gain are implicated in a range of adverse health conditions and life outcomes, particularly among minorities (Moore et al., 2009) who are disproportionately in poverty, face additional stressors, and consequently at higher obesity risk (Frederick et al., 2014).

The middle-pathways in Figure 1 show these pathways. The second goal of this study is thus to assess the sensitivity of adolescence and early adulthood for subsequent inflammation. We also assess whether minority inflammation disparities reflect differential body size trajectories and differential sensitivity by gender, while accounting for self-rated health—a key correlate of gender differences in CRP among adults aged 24–34 (Shanahan et al., 2014b).

Chains of Risk

Sequential biological and social exposures that elevate the probability of subsequent insults are referred to as "chains of risks" (Kuh et al., 2003). Consequently, one period may appear especially sensitive if continuity in body size trajectories is not accurately captured. BMI during childhood is correlated with BMI in early adulthood (Deshmukh-Taskar et al., 2005), consistent with the idea that body size growth and stability are a "chain of risks" integrating sensitive periods via body size trajectory rather than period-specific sensitivity. Body size at one period may thus be a proxy for subsequent body size. The chains of risk pathway in body size is indicated in the diagonal arrows linking body size at different periods, culminating in the adult obesity pathway to CVD risk in Figure 1. Therefore, our third goal is to assess how body size over time affects CVD risk via the CRP pathway in a multi-period model spanning from birth into adulthood. Due to the fact that reasonably high temporal resolution is required over long periods of time, only a few studies have been able to link early life course body size explicitly to inflammation in adulthood (Nazmi et al., 2009; Tzoulaki et al., 2008).

Understanding how body size at different periods predicts adult inflammation, or how body size in one period sets the stage for subsequent risk, is critical in identifying key life course intervention periods to offset the harmful inputs created by obesity exposure. Moreover, delineating these pathways is important for understanding racial minority health disparities, differential risk patterns over time for females and males, and the link between general health and CVD risk (Shanahan et al., 2014a).

Data & Methods

We use Add Health's Waves 1, 3, and 4 in-home evaluations. Add Health is an ongoing cluster stratified longitudinal study of 7–12th grade youth (ages 14–18) begun in 1994 from which a nationally representative sample of over 20,000 students was drawn from a large in-school study for in-home interviews in 1995 (grades 7–12; Wave 1). Respondents were reinterviewed in 2001–2002 as young adults (≈18–26; Wave 3), and then again in 2007–2008 (≈24–34; Wave 4). We did not utilize Wave 2 (grades 8–12) because it is located closely in time with Wave 1 (both are in the sensitive period of adolescence in our conceptual model) and adolescents who graduated were not interviewed again until Wave 3. The analysis used 7487 observations of white, African American, and Hispanic participants, with valid complex survey design information for statistical adjustment and who were not pregnant.

Measures

The primary dependent measure, high sensitivity C-reactive protein (hsCRP) in adulthood, was assayed from dried capillary whole blood spots (DBS) using a method adapted from (McDade et al., 2004) collected at Wave 4. Blood spots were collected during the in home visit and hsCRP was assayed using an adapted DBS sandwich ELISA procedure cross-validated with paired plasma samples (r=.98; N=80 matched serum samples). Sensitivity was 0.035 mg/L (plasma equivalent of 0.082), and intra-and inter-assay variation was 8.1% and 11%, respectively. Further technical specifications are available online (Whitsel et al., 2012). Serum equivalent hsCRP values were natural-logarithm (*ln*) transformed for the imputation and analytic models because the distribution was right-skewed (lnCRP; skewness decreased from 6.84 to −.07). Although we conducted sensitivity analyses with >3mg/L and >10mg/L cutoffs, the primary analyses utilize the full range of lnCRP. Notably, hsCRP concentrations have variability levels comparable to cholesterol and may be relatively stable within individuals across time (Ockene et al., 2001).

Because hsCRP is sensitive to anti-inflammatory drugs and recent illnesses, we adjust for both. The medications measure assesses whether the respondent took aspirin or aspirin-containing medications including cold and allergy medications or headache powders (examples included in the question wording) and whether the participant took other anti-inflammatory medications excluding acetaminophen, Tylenol, or aspirin-containing medications. The recent illnesses measure accumulated the following illnesses over the prior two weeks: (a) cold or flu-like symptoms such as sore throat, runny nose, or cough, (b) fever, (c) night sweats, (d) nausea, vomiting, or diarrhea, or (e) frequent urination.

The key theoretical variables utilize body size at birth (parent report, Wave 1; note that parent reports are reasonably accurate into adolescence [Walton et al., 2000]), during adolescence (Wave 1), early adulthood (Wave 3), and in adulthood (Wave 4). Height and weight were self-reported at Wave 1 and measured by trained interviewers at Waves 3 and 4. Interviewer measured height used a steel tape measure and carpenter square for alignment, and weight was measured using high capacity digital bathroom scale (for more information, see Entzel et al., 2009). BMI (kg/m^2) was calculated from height and weight and then categorized using WHO definitions: underweight (BMI<18.5), normal (18.5≤BMI<25), overweight (25≤BMI<30), obese class I (30≤BMI<35), obese class II (35≤BMI<40), and obese class III (BMI≥40). Age standardized percentile curves were calculated when youth were age 19 or younger using growth reference charts, and percentiles were used for categorization: underweight (%<5.0), normal (5≤%<85), overweight (85≤%<95), obese class I (95≤BMI<97), obese class II (97≤BMI<99), and obese class III (BMI≥99).

Birth weight coding relied on retrospective parent reports. In order to keep categories consistent over time, we utilized the same percentile classification categories as with BMI using the Add Health birth weight distribution. Importantly, reported results are consistent with analyses using traditional birth weight cutoffs (microsomia [<2500g], normal birth weight, and macrosomia [>4000g]). We present results using traditional BMI cutoffs to keep categories consistent across ages. Body size change measures are coded so that values

capture a decrease of 1+ categories, no categorization change, an increase of 1-body size category, or an increase of 2+ categories between birth→adolescence (Wave 1), adolescence→early adulthood (Waves 1 & 3), early adulthood→current adult (Waves 3 & 4). Change measures reflect body size *classification changes* and not specific changes in body size to facilitate inclusion of birth weight and BMI changes in terms of distributional references.

White youth are the reference category for indicators of whether the youth is African American or Hispanic/Latino using Wave 1 reports following Add Health recommended protocols for creating a single race measure from multiple discrete race items. For sex, males are the reference category. Self-reported health (SRH) uses a standard 5-category measure inquiring, “In general, how is your health?” where larger values represent poorer SRH. Age at Wave 4 was also included as a control variable. Descriptive statistics are reported in Table 1. (Table 1 about here)

Analysis Strategy

The analysis utilizes multiple imputation by chained equations (M=100) using the *ice* package for Stata (Royston, 2004, 2009), allowing us to tune the imputation model for each imputed variable’s measurement type. Complex survey design weights were included to ensure the imputations adhered to the analytic models. We did not impute on the dependent variable (lnCRP) though it was included in the imputation model to preserve the key intercorrelations. The analysis utilized OLS adjusted for complex survey design combined across imputed data sets (Little & Rubin, 2002). lnCRP was standardized in our analyses to facilitate interpretation.

Results

Primary Results

Complex design adjusted OLS coefficients for the multiple imputation analysis are presented in Table 2 (full results are available in an Online Appendix in Supplemental Table S1). Consistent with prior research using other data sources, Model M1 documents higher lnCRP values for African American and Hispanic adults versus whites, and for females relative to males (Khera et al., 2005; Wee et al., 2008), controlling for illnesses and medications and having restricted on pregnancy. Effect sizes indicate gaps of .13sd, .15sd, and .37sd for African Americans, Hispanics, and females, respectively. The race/ethnicity gaps manifest in different SRH (b=.21) in Model M2, with the African American gap reduced substantially ($p>.05$) and the Hispanic gap reduced to .09sd ($p<.05$). SRH and sex difference in lnCRP were largely unrelated.

Model M3 tests the fetal origins hypothesis by including birth weight and subsequent body size classification change into adolescence. Notably, children born in the smallest category had the lowest lnCRP (b=−.25), which increased in an approximately linear fashion across categories (Appendix Figure S1). The largest birth weights had lnCRP levels approximately .38sd higher than normal birth weight participants. Subsequent change also predicted lnCRP where decreasing a body size category was associated with lower adult

CRP (b=−.17), and 2+ category increase was associated with lnCRP levels nearly .7sd higher. As with body size categories, body size changes between waves were approximately linear (Figure S2). Moreover, the SRH coefficient decreased from .21 (M2) to .16, though the coefficient remained significant.

In models M4 and M5, which add body size and body size change categories for adolescence and young adults, respectively, a clear pattern emerges. First, the early life body size and change coefficients become non-significant when adolescent parameters are included (M4). Similar to M3, the effect magnitudes are large and approximately linear (Figures S1 and S2). However, the same pattern of reduction of prior terms to non-significance and significant effects for new coefficients again happens in the early adulthood model (M5). M5 then suggests that early adulthood (ages 18–24), not adolescence, is the key sensitive period for CRP at ages 24–33. Moreover, each iteration reduces the SRH coefficient until it is substantially smaller (.06sd) in M5, when the Hispanic coefficient is reduced to non-significance. In other words, the relationship between adult SRH and lnCRP is largely accounted for by early adult body size and body size change into adulthood, and the Hispanic-white disparity is completely accounted for.

Each model sequentially supports and then supplants one of the critical pathways. In Model M6 adult CRP is shown to reflect adult body size and large relatively recent changes in body size. Specifically, being overweight or obese is a significant physiological stressor, as is recent weight gain. Consequently, the reported effect sizes for larger bodies increase, as effects for each age period are included in the model. The overall pattern of results then points to the chains of risk hypothesis with correlated body size over time rather than lasting physiological insults being the primary explanatory pathway. To further clarify, we used contingency table analysis between body size periods and calculated tau-b and gamma to determine body size consistency over time, as shown in Figure 2 (which also includes a traditional birth weight categorization for comparison purposes). Body size is not strongly consistent between birth and adolescence, as expected. However, it is highly consistent from adolescence onwards. The result is an accumulation of body size, culminating in elevated adult hsCRP levels and increased CVD risk. These results suggest strongly interlinked body size classification from adolescence onwards, with change towards larger, less healthy bodies. This pattern constitutes a chain of risks whereby body size is correlated over time, what change happens tends towards obesity, with the physiological stress of having a larger age-proximate BMI increasing inflammation.

Ancillary Models & Robustness Checks

We conducted ancillary models and robustness checks. First, we determined that the key results reported in Table 2 were not simply capturing long-term body size exposure effects as reflected by the number of obesity classification measurements across age periods (Table S3). Second, we were concerned that durable differences in lnCRP by sex may reflect somewhat different physiological stress processes and pubertal development (Solorzano & McCartney, 2010). Based upon the generally linear pattern of results (Figures S1 & S2), we simplified the model in Table 2 such that categories were replaced by linear terms and then estimated sex-specific models (and imputations). Coefficient differences/similarities are

reported in Table 3 (full results available in Tables S5 and S6). The findings in Table 3 point to greater sensitivity to weight gain among women than men in a way consistent with chains of risk. In other words, greater sensitivity to weight gain across the early life course is implicated in adult women's elevated lnCRP levels relative to men. Rapid weight gain is thus more harmful for women and suggests that body size as a chain of risks may be more health damaging for young women. These findings were largely consistent when men were compared separately to parous and nulliparous women, suggesting that these sex differences are not solely driven by the difficulty of weight loss experienced by some women after giving birth (Table S7; e.g., Wang et al., 2011).

Further robustness checks indicate support for the chains of risk hypothesis when dichotomizing hsCRP as either high risk (>3; Table S3) or by very high values most likely indicative of recent illness (>10; Table S4), consistent with the reported results. Interactions by body size and body size change were tested, but no supporting evidence of this possibility was found (Figure S3), further supporting the chains of risk model. Results are also consistent when using traditional birth weight categories, when controlling for puberty status during adolescence, and when adjusting for completed education and parental education (Tables S8–S10). Taken together, these results point to body size as comprising a chain of risks that accumulate over time, and which females are more sensitive to when body size deviations produce weight gain.

Discussion

We have shown that multiple early life course periods predict an important CVD risk pathway in this national cohort of youth growing up during a period of explosive obesity change with dire implications for U.S. mortality. Our study supports findings from several international data sources and non-representative US data linking birth weight, adolescent, and early adulthood obesity to adult inflammatory risk (Bibbins-Domingo et al., 2007; Lee et al., 2012). This study also builds upon prior work by jointly accounting for early life course risk via birth weight, body size, body size changes, on adult CRP (Fraser et al., 2010; Nazmi et al., 2009; Tzoulaki et al., 2008). The findings suggest that early life course obesogenic weight gain and obesity status increase adult inflammation at ages 24–34. However, obesity in one period is highly correlated with more proximal obesity and BMI status, attenuating the prior life course period body-size-adult CRP link in a pattern most consistent with chains of risk.

Notably, we do not find strong direct support for the fetal origins hypothesis relative to more proximate body sizes in our most fully specified models. Prior research suggests a U-shape distribution of risk for accelerated growth where very low birth weight and very high birth weight children have a higher propensity for accelerated growth (Attard et al., 2013; McDade et al., 2014). In contrast, the effect of low birth weight was protective until adolescent BMI was controlled, after which it was not significant. These results may reflect a weak "thrifty phenotype" pathway for low birth weight status where accelerated growth results in later health body sizes. Consistent with this interpretation, birth weight was not strongly correlated with adolescent BMI. Unfortunately, these data can only provide a 'weak test' of the fetal origins hypothesis because growth data for early childhood were

unavailable. Gestational age, a measure not available in the Add Health, may be a better predictor of adult inflammation as preterm births are associated with in utero pathogen exposure, immature lung development, and hypocortisolism, a strong correlate of later obesity (Lynch & Smith, 2004).

Our findings were more supportive for macroscomia as a noxious exposure. Macrosomia can occur due to exposure to maternal obesity and gestational diabetes, which may shape offspring metabolic pathways via intrauterine hyperglycemic exposure (Kajantie, 2006; Wilcox et al., 2011). Moreover, women who exceed recommended gestational weight gain by the Institute of Medicine were more likely to have offspring with higher BMI, waist circumference, systolic blood pressure, and CRP levels at age 9 (Yessoufou & Moutairou, 2011). Macrosomic babies also have higher proinflammatory cytokine levels compared to normal birth weight offspring (Fraser et al., 2012). Unfortunately, neither maternal health, weight status during pregnancy, or gestational diabetes information is available in this data set. Our results suggest more detailed examination of the prenatal metabolic factors that contribute to subsequent metabolic and inflammatory life course processes among offspring as they transition to adulthood are needed.

Effect sizes for weight gains into higher obesity classifications are large over the early life course. Importantly, CRP increased with both period-specific body size and subsequent body size change, indicating both the dangers of at-risk body size and the physiological stress of body-size change. Though our study did not explicitly explore catch-up or accelerated growth experienced by youth born either micro or macrosomic, we found consistent evidence that being and becoming obese jointly increase risk. This suggests that CRP may not always be an ideal measure of long-term inflammation when participants have experienced recent weight changes. Specifically, our results consistently prioritize recent body size change and proximate body size versus earlier body sizes, although body size is highly correlated over time (Atègbo et al., 2006).

Not surprisingly, these results point to the need for early intervention (Howe et al., 2010). The best way to limit the obesity-CRP pathway to CVD is to prevent abnormal adipose weight gain and obesity. That is not news. However, the results are not so pessimistic that they suggest that all hope is lost if early life prevention opportunities are missed. Rather the key role of change and proximity suggest that returns to a normal-range body size at different periods may offset some inflammatory risk, but also raise the specter that subsequent rebounding weight gain could compound the harm. Thus, our results reinforce prior findings pointing to the need to mitigate risk early (Balagopal et al., 2005), but also support ongoing efforts to promote healthy eating and active life-styles across the life course (Juonala et al., 2013). More detailed and accurate temporal information, and experiments, are needed to determine whether body size reductions can be as affective at reducing inflammation as larger body sizes and body size increases are at increasing inflammation.

These results support prior studies suggesting that females are at higher inflammatory risk than males. For example, adolescent girls' obesity is associated with earlier timing of thelarche and menarche (Balagopal et al., 2005; Simon et al., 2008; Stewart et al., 2007), while boys' obesity is associated with delayed pubertal onset (Jasik & Lustig, 2008).

Furthermore, adolescent girls are at higher risk for increased adiposity relative to boys ages 15–19 (Solorzano & McCartney, 2010). Adolescent girls also have additional inflammatory risks associated from the pro-inflammatory hormone estrogen, while males' elevated testosterone is anti-inflammatory (Shanahan et al., 2013; Wozniak et al., 2009). Our ancillary analyses controlled for pubertal development, which did not alter our findings however, suggesting that differential sensitivity to weight gain and subsequent adult inflammation is unlikely to be due to puberty per se. The pattern of sensitivity, however, was consistent over time. Future research assessing the life course consequences of sex-specific disparities in adiposity and elevated inflammation are needed.

In addition, prior work has documented race/ethnic differences in CRP and links between global SRH and CRP (Khera et al., 2005; Shanahan et al., 2014a). Our results contribute to this larger literature on social variations in health by helping clarify the link between general health, race, and inflammation. Higher African American and Hispanic CRP levels relative to whites are grounded in body size trajectories that wholly reflect a general trend to poorer cardiometabolic health for African Americans, a trend partially reflected for Hispanics. For Hispanics in this cohort, body size in early adulthood accounted for the remaining gap after controlling for adult SRH. The SRH-CRP association was also greatly reduced across models as the chains of risk accumulated over periods. It is important to note that race differences in BMI patterns reflect a variety of factors such as lack of access to safe outdoor spaces, higher proximity to food desserts, and cultural diversity in valuation of body size in addition to widespread and diverse economic and social stressors indicative of the U.S.A's ongoing legacy of racial discrimination (Goosby & Heidbrink, 2013; Goosby et al., 2015; Ray, 2014; Story et al., 2008; Williams et al., 2012).

This study is not without limitations. We relied on parent reports of birth weight status collected during adolescence, though parent recall over this period has been shown to be accurate (Walton et al., 2000). It is also unclear how much bias is introduced by using BMI and these results would be strengthened by future studies more robust to the problems of BMI, such as measures of waist-to-hip or-height ratios (Walton et al., 2000). Weight gain in this cohort, however, is largely due to increasing adiposity and unhealthy weight gain (e.g., Burkhauser & Cawley, 2008). Moreover, though we have three waves of BMI data, our data only provides measures from early adolescence through adulthood such that we were unable to measure the timing of growth and increased adiposity during early and middle childhood. Additionally, CRP is measured only at Wave 4 so we were unable to study CRP change and BMI change jointly. This study does, however, have a number of strengths. Our study is one of only a small number assessing birth weight status along with growth as youth transition into adulthood. We were able to account for both birth weight and body size change at multiple periods across the early life course. Add Health, when properly weighted, is also nationally representative of a cohort that has experienced unprecedented obesity levels.

Conclusion

In conclusion, the goal of this study was to clarify how body size over the early life course contributes to CVD risk via an inflammatory pathway for a nationally representative cohort of adults who have experienced skyrocketing obesity rates. Though obesity status at earlier

periods is highly correlated both with subsequent overweight, obesity, and inflammation, there is also potential to offset this particular risk factor via interventions (Gordon-Larsen et al., 2004a; Lee et al., 2012). Doing so for young women may be particularly important as evidence suggests that women are more sensitive to the BMI-chains-of-risk model we employed. Moreover, differential body size trajectories from birth explain inflammatory differences for African American's relative to whites, and from early adulthood for Hispanics. Life course research in the future should consider chains of risk models that seek to understand how risks are correlated and interdependent in the study of health disparities within and across diverse populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights

- Early life course body size changes predict adult hsCRP.
- Obesity at each period, and body size between periods, is associated with hsCRP.
- Birth weight-adult inflammation risk is mediated by later BMI and BMI change.
- Inflammatory risk can be offset by weight loss.
- Early BMI trajectories account for Black and Hispanic-white inflammation disparities.

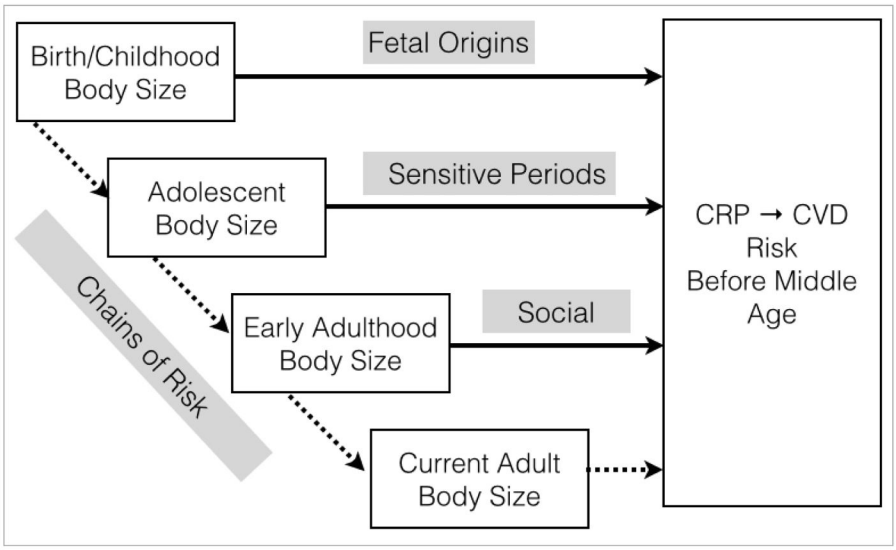

Figure 1.
Conceptual Mode

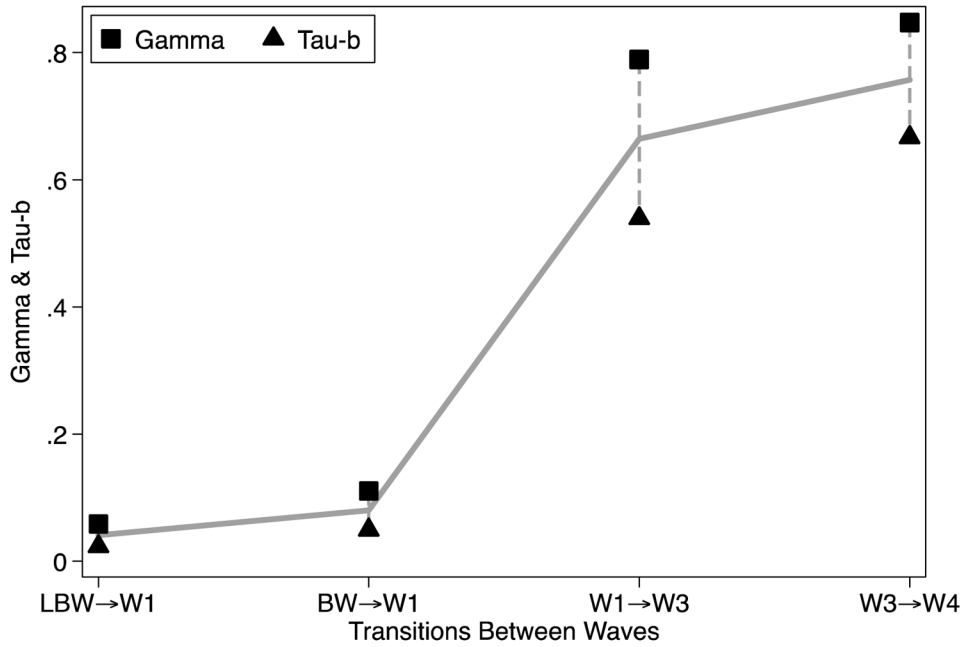

Figure 2. Contingency Table Analysis of State Transitions in Body Size Classification

Notes: LBW refers to traditional low/normal/macrosomic birth weight categories. BW refers to the categories used in the analysis. W1/3/4 refer to adolescent, early adulthood, and current age respectively.

Table 1

Descriptive statistics (unweighted; N=7487)

Variable	Obs	%Obs.'d	Mean	Std. Dev.	Min	Max
ln(CRP)	7487	100	0.71	1.38	−6.21	5.32
Black (white ref.)	7487	100	0.22		0	1
Hispanic (white ref.)	7487	100	0.17		0	1
Female	7487	100	0.55	0.50	0	1
Illness count	7487	100	0.41	0.72	0	5
Medication count	7487	100	0.35	0.60	0	2
Age, current	7485	100	28.10	1.65	24	33
Self rated health, current	7487	100	2.36		1	5
Birth Weight (BW)						
Underweight (by BMI%)	6157	82	0.07		0	1
Overweight (by BMI%)	6157	82	0.10		0	1
Obese I (by BMI%)	6157	82	0.02		0	1
Obese II (by BMI%)	6157	82	0.02		0	1
Obese III (by BMI%)	6157	82	0.01		0	1
BW to Ad. %-tile Change						
−1(+)categories	5991	80	0.13		0	1
+1 categories	5991	80	0.18		0	1
+2(+) categories	5991	80	0.12		0	1
Adolescent BMI						
Underweight	7271	97	0.02		0	1
Overweight	7271	97	0.17		0	1
Obese I	7271	97	0.04		0	1
Obese II	7271	97	0.06		0	1
Obese III	7271	97	0.02		0	1
Adolescent to Early Adult BMI						
−1(+)categories	6898	92	0.11		0	1
+1 categories	6898	92	0.26		0	1
+2(+) categories	6898	92	0.09		0	1

Variable	Obs	%Obs.'d	Mean	Std. Dev.	Min	Max
Early Adult BMI						
Underweight	7093	95	0.03		0	1
Overweight	7093	95	0.25		0	1
Obese I	7093	95	0.12		0	1
Obese II	7093	95	0.07		0	1
Obese III	7093	95	0.04		0	1
Early Adult to Current Adult BMI						
−1(+)categories	7041	94	0.07		0	1
+1 categories	7041	94	0.34		0	1
+2(+) categories	7041	94	0.10		0	1
Current Adult BMI						
Underweight	7416	99	0.01		0	1
Overweight	7416	99	0.29		0	1
Obese I	7416	99	0.19		0	1
Obese II	7416	99	0.10		0	1
Obese III	7416	99	0.10		0	1

Table 2

Standardized ln(CRP) coefficients

Parameter	M1	M2	M3	M4	M5	M6
African American	0.13**	0.08	0.05	0.03	−0.01	−0.02
Hispanic	0.15***	0.09*	0.08*	0.08*	0.06	0.06
Female	0.37***	0.35***	0.38***	0.36***	0.35***	0.35***
Illness count	0.18***	0.14***	0.14***	0.14***	0.14***	0.14***
Medication count	0.10***	0.08***	0.08***	0.09***	0.08***	0.08***
Age, current	0.02	0.01	0.02*	0.00	0.01	0.01
SRH, current		0.21***	0.16***	0.13***	0.06***	0.06***
Birth Weight (BW)						
Underweight (by BMI%)			−0.26**	0.04	0.08	0.08
Overweight (by BMI%)			0.16**	−0.13	−0.16*	−0.16*
Obese 1 (by BMI%)			0.19	−0.16	−0.18	−0.18
Obese 2 (by BMI%)			0.27**	−0.21	−0.25	−0.24
Obese 3 (by BMI%)			0.38**	−0.30	−0.33*	−0.32*
BW to Ad. %-tile Change						
−1(+)categories			−0.17**	0.14	0.14	0.14
+1 categories			0.32***	−0.01	−0.03	−0.03
+2(+) categories			0.64***	0.04	−0.05	−0.03
Adolescent BMI						
Underweight				−0.50***	−0.13	−0.10
Overweight				0.32***	−0.02	−0.05
Obese 1				0.51***	0.00	−0.04
Obese 2				0.69***	−0.09	−0.16
Obese 3				0.87***	−0.06	−0.17
Adolescent to Early Adult BMI						
−1(+)categories				−0.10	0.09	0.10

Parameter	M1	M2	M3	M4	M5	M6
+1 categories				0.29***	0.04	0.02
+2(+) categories				0.58***	−0.06	−0.10
Early Adult BMI						
Underweight					−0.30**	−0.05
Overweight					0.30***	0.04
Obese 1					0.66***	0.18
Obese 2					1.07***	0.35
Obese 3					1.42***	0.46
Early Adult to Current Adult BMI						
−1(+)categories					−0.38***	−0.11
+1 categories					0.39***	0.11
+2(+) categories					0.82***	0.26*
Current Adult BMI						
Underweight						−0.24
Overweight						0.34***
Obese 1						0.55***
Obese 2						0.86***
Obese 3						1.06***
Constant	−0.35***	−0.79***	−0.82***	−0.85***	−0.89***	−0.90***

*p<0.05,

**p<0.01,

***p<0.001

Notes: Standard errors are shown in Supplementary Table S1.

Table 3

P-values comparing Male-Female coefficients (full results in Supplemental Tables S4–S5)

	1		2		3		4		5		6	
	Diff	**P-value**	**Diff**	**P-value**	**Diff**	**P-value**	**Diff**	**P-value**	**Diff**	**P-value**	**Diff**	**P-value**
African American	F>M	**0.012**	F>M	**0.029**		0.196		0.335		0.840		0.685
Hispanic		0.119		0.200		0.230		0.263		0.374		0.417
Illness count		0.677		0.744		0.722		0.727		0.702		0.643
Medication count		0.129		0.129	M>5	**0.036**	M>F	**0.025**		0.060		0.076
Age, current		0.249		0.437		0.275		0.078		0.056		0.054
SRH, current				0.664		0.387		0.084	M>F	**0.019**	M>F	**0.013**
Birth weight cat.						0.133		0.966		0.772		0.722
Change: birth-ad.					F>M	**0.048**		0.911		0.892		0.850
BMI cat., adolescence								0.396		0.139		0.140
Change: ad.-early adult							F>M	**0.004**		0.114		0.105
BMI cat., early adult										0.218		0.182
Change: early adult-current									F>M	**0.018**		0.852
BMI cat., current												0.494